DE-ESCALATION OF COMPLEX INSULIN REGIMENS WHILE PRESERVING GOOD GLYCEMIC CONTROL IN TYPE 2 DIABETIC PATIENTS

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PhD Thesis

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Relevant publications

Full papers

I**. Taybani Z**, Bótyik B, Katkó M, Gyimesi A, Várkonyi T. Simplifying Complex Insulin Regimens While Preserving Good Glycemic Control in Type 2 Diabetes. Diabetes Therapy. 2019;10(5):1869-1878 **(impact factor: 2.827)**

II. **Taybani Z**, Bótyik B, Katkó M, Gyimesi A, Várkonyi T, Kempler P. De-escalation of complex insulin regimens in well controlled patients with type 2 diabetes in everyday clinical practice. Diabetes, Stoffwechsel und Herz. 2019;28(6):354-359 **(impact factor: 0.082)**

III. **Taybani Z**, Bótyik B, Katkó M, Gyimesi A, Kempler P, Várkonyi T. Komplex inzulinkezelési rezsimek deeszkalációja a jó glikémiás kontroll megőrzésével 2-es típusú diabetes mellitusban [De-escalation of complex insulin regimens while preserving good glycemic control in type 2 diabetes]. Diabetologia Hungarica. 2020. (in press)

Published abstracts

Taybani Z, Bótyik B, Katkó M, Gyimesi A. Simplifying complex insulin regimens with preserving good glycemic control in type 2 diabetes. Diabetes Technology & Therapeutics. 2018,20(S1):145-146.

Taybani Z, Bótyik B, Katkó M, Gyimesi A. Simplification of complex insulin regimens with preserving good glycaemic control in type 2 diabetes. Diabetologia. 2018,61(S1):S414.

Taybani Z, Bótyik B, Gyimesi A, Katkó M. Komplex inzulinkezelési rezsimek egyszerűsítése a jó glikémiás kontroll megőrzésével 2-es típusú diabetesben [Simplifying complex insulin regimens with preserving good glycemic control in type 2 diabetes]. Diabetologia Hungarica. 2018,26(S1):95-96.

Veres A, Bótyik B, Fehértemplomi K, Szerencsi R, **Taybani Z.** A túlkezelés rizikója hypoglykaemizáló szerekkel kezelt idős 2-es típusú diabetes mellitusos betegekben [Risk of

potential overtreatment in older adults with type 2 diabetes treated with hypoglycemic medications]. Diabetologia Hungarica. 2019,27(S1):63-64.

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Abbreviations

IDF: International Diabetes Federation

T2D: Type 2 diabetes

MDI: Multiple daily insulin injections

FRC: fixed-ratio combination

GLP-1-RA: glucagon-like peptide-1 receptor agonist

TDD: total daily insulin dose

BMI: body mass index

MF: metformin

BV: baseline visit

SMBG: self-measured blood glucose

SD: standard deviation

IQR: interquartile range

CGM: continuous glucose monitoring

SGLT2I: sodium-glucose cotransporter-2 inhibitor

SAE: serious adverse event

1. Introduction

There are 463 million people living with diabetes in the World and there will be 700 million in 2045 according to estimates of the International Diabetes Federation (IDF) [1]. In spite of the introduction of newer non-insulin type glucose lowering agents (e.g. glucagon-like peptide-1 receptor agonists [GLP-1 RAs] or sodium-glucose cotransporter-2 inhibitors [SGLT2Is]) insulins used in complex regimens are still the mainstay of antidiabetic therapy.

Patients with type 2 diabetes (T2D) suffering from severe hyperglycemia are often put on multiple daily insulin injections (MDI). If the glucose toxicity resolves, the complex regimen may potentially be simplified, but there are no specific guidelines regarding this procedure and a lot of patients are left on MDI for years meanwhile a considerable proportion of them become overtreated [2,3,4]. Some of the patients using MDI were assigned to this treatment earlier when there were no therapeutic alternatives to basal-bolus therapy. Beyond severe hyperglycemia MDI is also often applied for transient reasons (for example surgery, polytraumatism, severe infection etc.) however a lot of these patients are left on the complex medication in spite of the cessation of the indication.

In general overtreatment is defined as the use of a treatment even when the potential harms exceed the possible benefits [5]. Patients with T2D who are treated with oral or injectable hypoglycemic agents too aggressively and have HbA_{1c} values permanently lower than their individual target range are considered to be overtreated and overcontrolled. Overtreatment of T2D with hypoglycemic medications particularly in frail and elderly patients with comorbidities is potentially harmful because it may increase the risk of hypoglycemia and weight gain, poses excess treatment burden on them and worsens their quality of life. Many recent studies demonstrated that overtreatment is a common but generally unrecognized problem in patients with T2D abroad and even in Hungary [6,7,8, 9].

Another type of overtreatment is when well-controlled T2D patients are using unnecessarily complex insulin regimens instead of simpler alternatives which would ensure the same glycemic control with significantly less treatment burden.

Deintensification or de-escalation is a process to simplify, reduce or withdraw medications to avoid overtreatment in order to reduce the risk of polypharmacy and associated adverse events.

In spite of the high rates of overtreatment with complex medications, deintensification in everyday clinical practice is infrequent [10,11,12,13]. On the other hand evidence based strategies to prevent overtreatment in people with T2D and to simplify MDI regimens are still scarce [14,15,16]. Moreover, there are many barriers to deintensification at the healthcare professional, general public, and healthcare system levels [17]. A first step towards preventing the detrimental medical consequences of and the impaired quality of life caused by overtreatment would be to analyze follow-up trials that are designed to evaluate the outcomes of treatment de-escalation.

Fixed-ratio combinations (FRCs) consisting of a long-acting basal insulin and a GLP-1-RA represent a novel approach to insulin therapy. One of these combinations, IDegLira is the titratable fixed-ratio combination of a second-generation ultra long-acting basal insulin analog (insulin degludec, 100 units/mL) and the GLP-1-RA liraglutide (3.6 mg/mL). Compared to basal-bolus therapy IDegLira has similar glycemic efficacy with less hypoglycemic risk and more favourable effect on body weight in T2D patients previously treated unsuccessfully with a basal insulin plus oral glucose lowering agents [18]. On the basis of these observations it is reasonable to think that IDegLira can be a potential tool for simplifying complex insulin regimens in selected T2D patients.

Our hypothesis was that in everyday clinical practice switching from MDI to once-daily IDegLira in relatively well controlled ($HbA_{1c} \leq 7.5\%$) T2D subjects using a low total daily insulin dose (TDD) is feasible, safe and effective. We performed a prospective clinical trial to confirm our hypothesis [19,20,21].

Our main goals were:

- to describe the characteristics of those well-controlled T2D patients treated with MDI who are eligible for medication de-escalation,
- to demonstrate that in everyday clinical practice switching from MDI to IDegLira in selected T2D patients is feasible,
- to prospectively examine the safety of switching from MDI to once-daily IDegLira in relatively well controlled subjects with T2D,
- to prospectively examine the glycemic efficacy of switching from MDI to once-daily IDegLira in relatively well controlled subjects with T2D,

- to examine the effect of de-escalation on body weight, risk of hypoglycemia and daily insulin need.

2. Patients and methods

2.1. Trial design and participants

This was a real-world setting, prospective, single-arm clinical trial of patients with T2D. It was conducted at the Diabetes Center of the Békés County Central Hospital – Dr. Réthy Pál Member Hospital (Békéscsaba, Hungary) from 2016 January.

The T2D patients included were ≥18 years old and had detectable random, non-fasting serum C-peptide levels (≥1.1 ng/mL; normal range 1.1-4.1 ng/mL) and an HbA_{1c}≤7.5%. The patients enrolled were treated with MDI (stable daily doses of insulin had been administered at least for 90 days prior to the baseline visit [BV]) ± metformin (MF) and were using relatively low total daily insulin dose [TDD]. At BV low TDD was defined as TDD≤70 IU/day and TDD≤0.6 IU/kg/day at the same time. Clearly overinsulinised individuals who had severe or repeated symptomatic hypoglycemia during the month before BV using TDD≤70IU/day and 0.8>TDD>0.6 IU/kg/day could also be admitted to the study. As IDegLira is a relatively costly medicine in Hungary even though it is partially covered by health insurance, only those patients were enrolled who accepted the probable expenses of the medication.

Exclusion criteria included type 1 diabetes, treatment of T2D with any glucose lowering agents other than insulin or metformin during the 90 days before BV, active cancer, anaemia (haemoglobin <100g/l) and acute or chronic kidney disease with an estimated glomerular filtration rate <30 mL/min/1.73 m^2.

2.2. Procedures

At BV previous insulins were stopped and once daily IDegLira was started at any time, independent of meals, repeated approximately at the same time each day. In most cases IDegLira was administered in the morning, but some patients used it at bedtime. IDegLira was started with 16 units (each unit contains 1 unit of insulin degludec and 0.036 mg of liraglutide)

and patients titrated every 3 days with 2 units to achieve a pre-breakfast self-measured blood glucose (SMBG) range of 5-6 mmol/L [22].

The maximum daily dose of IDegLira was 50 units. Metformin was initiated or continued and titrated up with 500 mg weekly to 3000 mg or to the maximal tolerated dose. Patients were asked to test blood glucose daily in a structured manner (one measurement before breakfast and one test before lunch or dinner) and to record SMBG measurements in their diary.

Participants returned to the Diabetes Center 2 weeks after switching of therapy, at which point self-titration and adverse events were rechecked (Visit 0). Patients were monitored over the course of their routine diabetes care. Clinical characteristics were assessed at baseline and at 3, 7 and 12 months after initiating IDegLira. In a subgroup of patients we performed professional continuous glucose monitoring (CGM) at baseline before switching to IDegLira and 3 months after the initiation of the treatment to compare the effects of MDI regimens and IDegLira on different parameters of glycemic control and variability. So far the 3 months and 7 months data were analysed and published.

2.3. Outcome measures

The primary endpoint was the change in HbA_{1c} at 3 months (Visit 1), at 7 months (Visit 2) and at 12 months (Visit 3) from baseline. Secondary outcomes included change in body weight, TDD, and incidence of documented (SMBG<3.9 mmol/L) or symptomatic hypoglycemia during the follow-up. Severe hypoglycemia requiring external assistance and clinically meaningful adverse events were also recorded.

2.4. Statistical analysis

Statistical analysis was performed using GraphPad Prism 6 software (GraphPad Software, San Diego, CA, USA). Data are presented as mean ± standard deviation (SD) or median with 25^{th} and 75^{th} percentiles (interquartile range, IQR) for continuous variables in case of normal and non-normal distribution, respectively, and as n (%) for frequency data. During the analysis of the 3 months data clinical and demographic variables measured before and after switching therapy were compared using two-tailed paired t-test for normal distributed data and Wilcoxon signed rank test for non-normal distributed data. P values <0.05 were considered to indicate

statistical significance. During the analysis of the 7 months data variables at baseline, at 3 months and 7 months were compared using repeated measures ANOVA with Tukey post-hoc test for data with normal distribution and Friedman test with Dunn post-hoc test for data with non-normal distribution. P values < 0.05 were considered to indicate statistical significance.

2.5. Ethical approvement, informed consent

Our trial conformed to the recommendations of the Declaration of Helsinki and the International Council on Harmonization Good Clinical Practice norms with regard to medical research in humans. The study protocol was approved by the local institutional and by the Hungarian National Medical Research Council's ethical review board. All patients provided written informed consent form before they were enrolled.

3. Results

3.1. Results of the 3 months analysis

Between February 2016 and July 2018, 69 T2D patients meeting the trial's inclusion criteria were switched to IDegLira. Soon after switching, 3 patients ceased the therapy for financial reasons, 1 patient gradually reduced and finally stopped IDegLira due to low SMBG values before visit 1 and remained well controlled on metformin monotherapy, 1 patient discontinued the medication after a few days due to moderate adverse gastrointestinal effects, and 2 patients did not return to the scheduled control. Thus, 62 patients (baseline age 64.06 ± 10.24 years, HbA_{1c} 6.42 ± 0.68%, body mass index [BMI] 33.53 ± 6.90 kg/m^2, body weight 93.81 ± 19.26 kg, TDD 43.31 ± 10.99 IU/day, insulin requirement 0.47 ± 0.13 IU/kg, duration of diabetes 10.84 ± 7.50 years, mean ± SD) attended an assessment 3 months after initiating IDegLira (visit 1) and were included in the analysis (Table 1) [19,20].

At baseline, 49 (79%) patients were on a basal-bolus regimen using 1 dose of basal insulin and 3 doses of prandial insulin (38 used human and 11 used an analog insulin), and 13 (21%) patients were treated with two or three doses of human or analog premix insulins (Fig. 1). At BV, 38 (61%) patients were taking MF (median dose was 1500 [0–2000] mg), the mean number of insulin injections daily was 3.69 ± 0.69, and the mean C-peptide was 4.00 ± 2.52 ng/mL.

Table 1 Patient characteristics at baseline and at 3 months of follow-up

Characteristics	At baseline	At 3 months (visit 1)	Estimated mean difference (95% CI)	*p* value*
HbA1c (%)	6.42 (0.68)	6.12 (0.65)	− 0.30 (− 0.42 to − 0.18)	$p < 0.0001$
Body weight (kg)	93.81 (19.26)	90.70 (19.12)	− 3.11 (− 4.04 to − 2.18)	$p < 0.0001$
BMI (kg/m2)	33.53 (6.90)	32.39 (6.71)	− 1.14 (− 1.47 to − 0.81)	$p < 0.0001$
Total daily insulin dose (units)	43.31 (10.99)	20.76 (6.60)	− 22.55 (24.96–20.14)	$p < 0.0001$
Insulin requirement (IU/kg)	0.47 (0.13)	0.23 (0.08)	− 0.24 (− 0.27 to − 0.21)	$p < 0.0001$
Metformin dose (mg/day)	1500 [0–2000]	2000 [1000–2000]	NA	$p < 0.0001$

Values are the mean (SD) or the median [IQR]

* From the Wilcoxon signed-rank test for metformin dose and the paired *t* test for other parameters

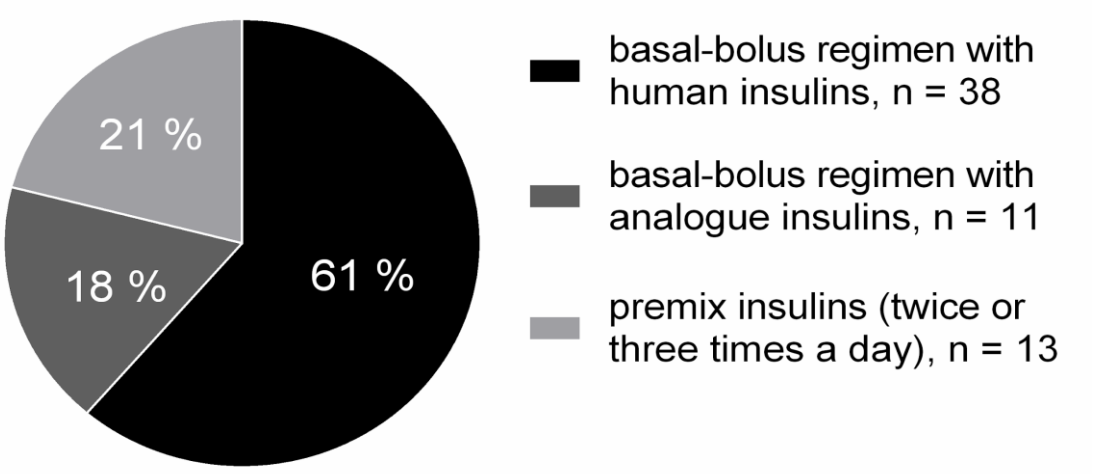


Fig. 1 Proportions of patients using different kinds of insulin regimens at baseline

After a mean follow-up of 99.2 days, HbA_{1c}, body weight, and BMI decreased significantly (Figs. 2, 3).

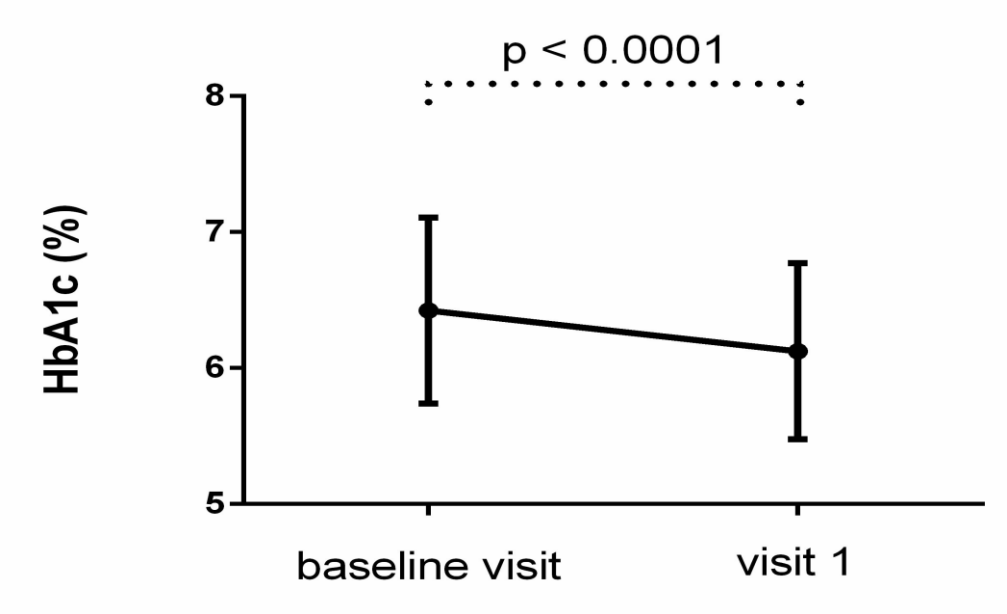


Fig 2 HbA_{1c} (mean±SD) of the patients at baseline and 3 months later

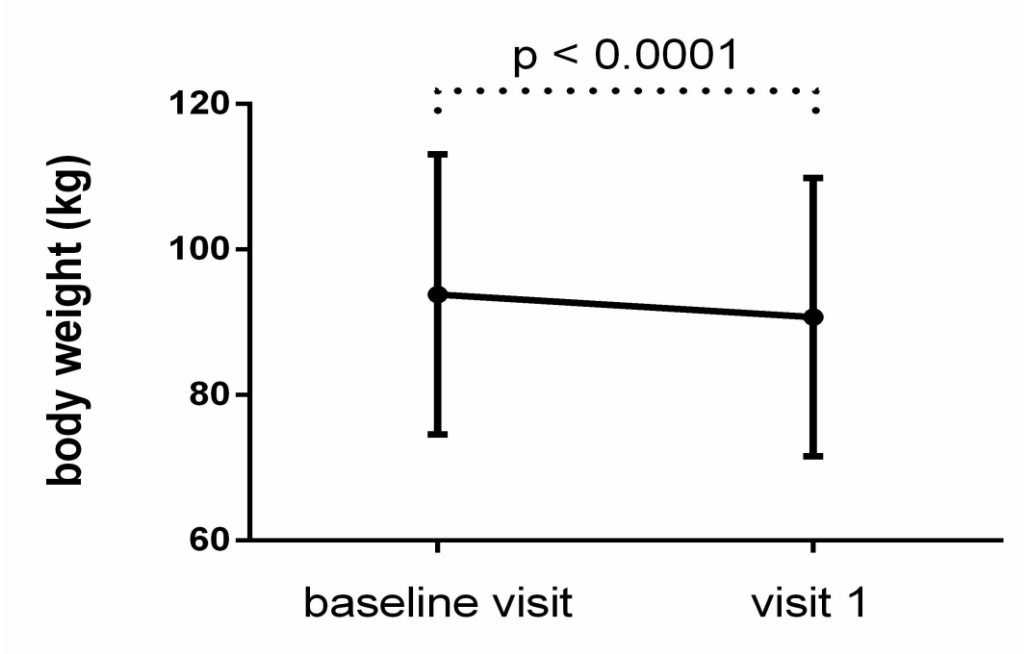


Fig 3 Body weight (mean±SD) of patients at baseline and 3 months later

Mean HbA_{1c} decreased by 0.30% to 6.12 ± 0.65% ($p < 0.0001$), body weight decreased by 3.11 kg to 90.70 ± 19.12 kg ($p < 0.0001$), and BMI decreased by 1.14 kg/m^2 to 32.39 ± 6.71 kg/m^2 ($p < 0.0001$).

After 3 months of follow-up, the mean dose of IDegLira was 20.76 ± 6.60 units (the mean dose of liraglutide was 0.75 mg), the median dose of metformin was 2000 [1000–2000] mg, and the mean insulin requirement decreased to 0.23 ± 0.08 IU/kg.

IDegLira + metformin combination therapy was found to be safe and generally well tolerated. Transient gastrointestinal adverse events (lack of appetite, nausea, or diarrhea) were reported by 14 patients (22.5%), and 1 patient had transient dysthymia. Only one serious adverse event (SAE) occurred (acute non-ST segment elevation myocardial infarction), which in our opinion was not related to the IDegLira therapy.

During the month before BV, 28 patients (45%) had at least one episode of documented (self-measured plasma glucose < 3.9 mmol/L) or symptomatic hypoglycemia, while only 6 (9.67%) patients reported a total of 13 documented (1 asymptomatic and 12 mild) episodes during the follow-up. Severe hypoglycemia requiring external assistance did not occur (Fig. 4).

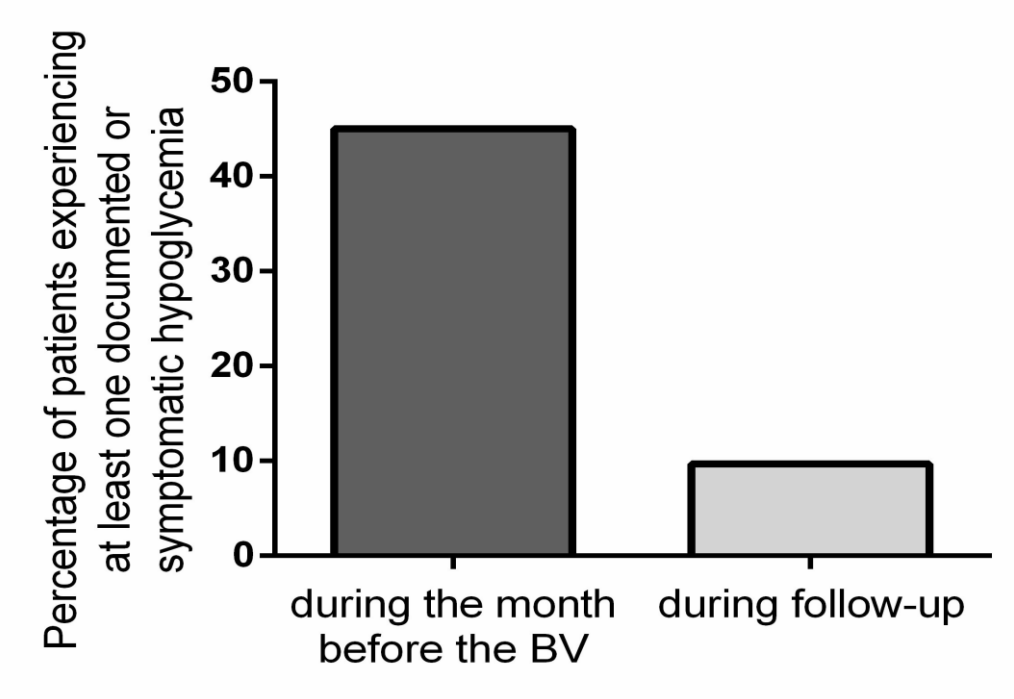


Fig 4 The percentage of patients experiencing at least one episode of documented (self-measured blood glucose<3.9 mmol/L) or symptomatic hypoglycemia during the month before baseline visit (BV) was 45%, whereas the corresponding percentage at the 3-month follow-up was 9.7%.

The mean daily number of injections changed from 3.69 to 1, and the patients reported a substantial decrease in the number of blood glucose tests performed each day.

The proportions of the patients who had achieved $HbA_{1c} \leq 7\%$ and $HbA_{1c} \leq 6.5\%$ were 92% ($n = 57$) and 66% ($n = 41$), respectively (Fig. 5). The proportions of the patients who achieved $HbA_{1c} \leq 7\%$ and $HbA_{1c} \leq 6.5\%$ without any weight gain were 79% ($n = 49$) and 53% ($n = 33$), respectively. The proportions of the patients who attained $HbA_{1c} \leq 7\%$ and $HbA_{1c} \leq 6.5\%$ without hypoglycemia were 82.25% ($n = 51$) and 56.45% ($n = 35$), respectively. Finally, the proportions of the patients who realized $HbA_{1c} \leq 7\%$ and $HbA1c \leq 6.5\%$ without weight gain and without hypoglycemia were 72.58% ($n = 45$) and 46.77% ($n = 29$), respectively.

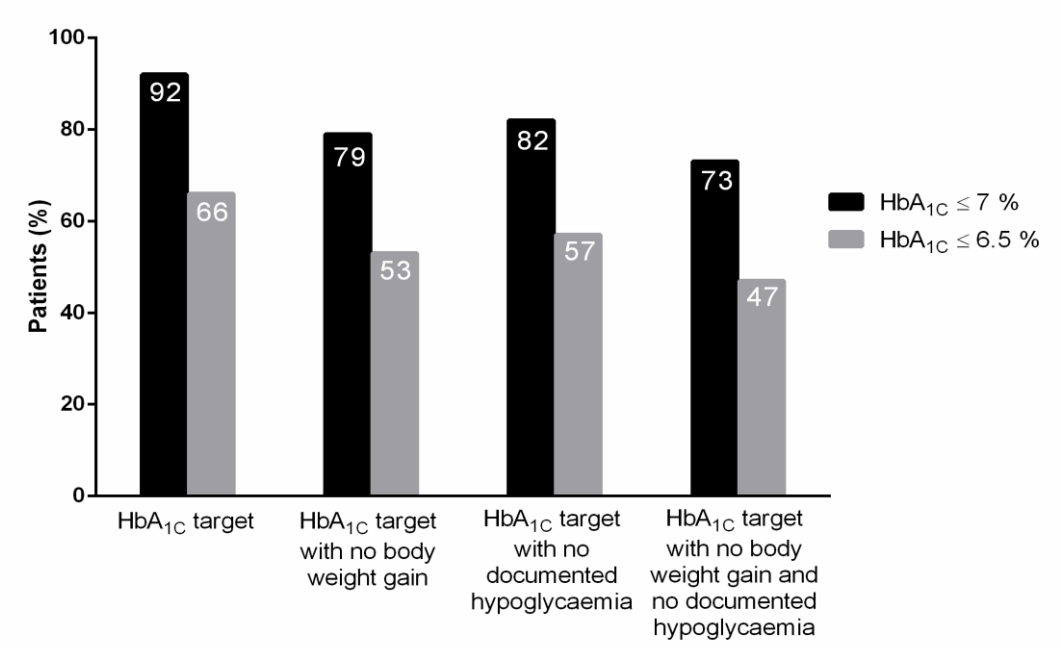


Fig 5 Proportions of patients who had achieved various glycemic targets at visit 1

3.2. Results of the 7 months analysis

Between February 2016 and July 2019, 89 MDI treated patients with T2D meeting the trial's inclusion criteria were switched to IDegLira. [21] Soon after switching 4 patients ceased the therapy due to financial reasons, 3 patients gradually reduced and finally stopped IDegLira due to low SMBG values before visit 1, and remained well-controlled on non-insulin therapy, 3 patients discontinued IDegLira in a few days due to moderate gastrointestinal adverse effects

(abdominal pain, nausea) and 3 patients did not return to the scheduled controls. 8 patients on IDeglira were still before Visit 2 so their data could not be included in the analysis. Finally 68 patients (55% female, baseline age 64.01 ± 9.72 years, HbA_{1c} 6.36 ± 0.7%, BMI 33.48 ± 6.73 kg/m^2, body weight 93.88 ± 19.18 kg, TDD 43.77 ± 11.3 IU/day, insulin requirement 0.47 ± 0.12 IU/kg, duration of diabetes 10.29 ± 7.49 years, mean±SD) completed visit 2 before August 2019 and were included in this analysis (Table 2).

Table 2 Patient characteristics at baseline and at 3 and 7 months of follow-up

Characteristics	At baseline	At 3 months (visit 1)	At 7 months (visit 2)	Estimated mean difference (95% CI)	p value *
HbA1c (%)	6.36 (0.71)	6.08 (0.62)	6.2 (0.64)	v1-bv: -0.28 (-0.42 ─ -0.13) v2-bv: -0.16 (-0.33 ─ 0.01) v2-v1: 0.11 (-0.03 ─ 0.26)	<0.0001 0.07 0.14
Body weight (kg)	93.88 (19.18)	90.52 (19.08)	89.61 (19.31)	v1-bv: -3.36 (-4.41 ─ -3.30) v2-bv: -4.27 (-5.65 ─ -2.89) v2-v1: -0.91 (-1.68 ─ -0.14)	<0.0001 <0.0001 0.02
BMI (kg/m^2)	33.48 (6.73)	32.25 (6.58)	31.93 (6.64)	v1-bv: -1.22 (-1.59 ─ -0.85) v2-bv: -1.55 (-2.04 ─ -1.06) v2-v1: -0.33 (-0.60 ─ -0.06)	<0.0001 <0.0001 0.01
Total daily insulin dose (units)	43.77 (11.3)	20.69 (6.47)	21.44 (7.64)	v1-bv: -23.09 (-26.02 ─ -20.16) v2-bv: -22.34 (-25.19 ─ -19.49) v2-v1: 0.75 (-0.26 ─ 1.76)	<0.0001 <0.0001 0.18
Insulin requirement (IU/kg)	0.47 (0.12)	0.23 (0.07)	0.24 (0.08)	v1-bv: -0.24 (-0.27 ─ -0.21) v2-bv: -0.23 (-0.26 ─ -0.20) v2-v1: 0.01 (-0.00 ─ 0.02)	<0.0001 <0.0001 0.06
Metformin dose (mg/day)	1600 [0-2000]	2000 [1000-2000]	2000 [1000-2000]	v1-bv: NA v2-bv: NA v2-v1: NA	0.001 <0.001 0.99

Values are the mean (SD) or the median [IQR]

* From the Friedman test with Dunn post-hoc test for metformin dose and from repeated measures ANOVA with Tukey post-hoc test for other parameters

At BV 44 (65%) patients were taking MF (median dose was 1600 mg), the mean number of daily insulin injections was 3,75 ± 0,63 and mean C-peptide was 3.91 ± 2.48 g/mL.

At baseline 56 (82%) patients were on a basal-bolus regimen using one dose of basal and 3 doses of prandial insulins (63% used human and 19% used analog insulins), 12 (18%) patients were treated with 2 or 3 doses of human or analog premix insulins (Fig. 6).

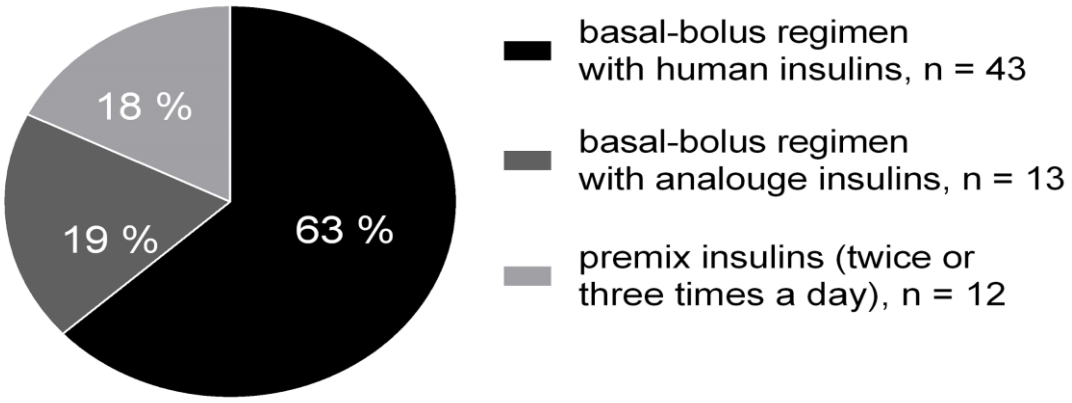


Fig. 6 Proportions of patients using different kinds of insulin regimens at baseline

Visit 2 was performed 7 months after the baseline visit (the mean follow-up was of 220 days). HbA_{1c} decreased from 6.36 ± 0.71% at baseline to 6.08 ± 0.62% at visit 1 (estimated mean difference between baseline and visit 1: -0.28 [-0.42 ─ -0.13], $p<0.0001$) and to 6.20 ± 0.64% at visit 2 (estimated mean difference between baseline and visit 2: -0.16% [-0.33 - 0.01], $p=0.07$) (Fig. 7).

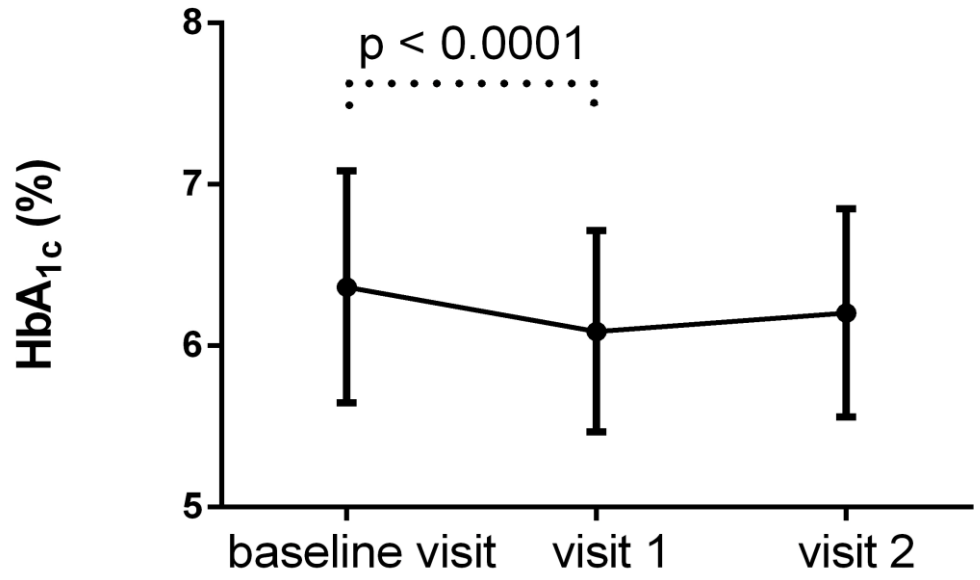


Fig. 7 HbA_{1c} (mean±SD) of patients at baseline and 3 and 7 months later

Body weight decreased from 93.88 ±19.18 kg at baseline to 90.52 ± 19.08 kg at visit 1 (estimated mean difference between baseline and visit 1: -3.36 [-4.41 ─ -3.30], p<0.0001) and to 89.61 ± 19.31 kg at visit 2 (estimated mean difference between baseline and visit 2: -4.27 [-5.65 ─ -2.89], p<0.0001).

BMI decreased from 33.48 ± 6.73 kg/m^2 at baseline to 32.25 ± 6.58 kg/m^2 at visit 1 (estimated mean difference between baseline and visit 1: -1.22 [-1.59 ─ -0.85], p<0.0001) and to 31.93 ± 6.64 kg/m^2 at visit 2 (estimated mean difference between baseline and visit 2: -1.55 [-2.04 ─ -1.06], p<0.0001]) (Figs. 8,9).

After 7 months of follow-up mean dose of IDegLira was 21.44 ± 7.64 units (mean dose of liraglutide was 0.77 mg), median dose of metformin was 2000 mg, and mean insulin requirement decreased from 0.47 ± 0.12 IU/kg to 0.24 ± 0.08 IU/kg.

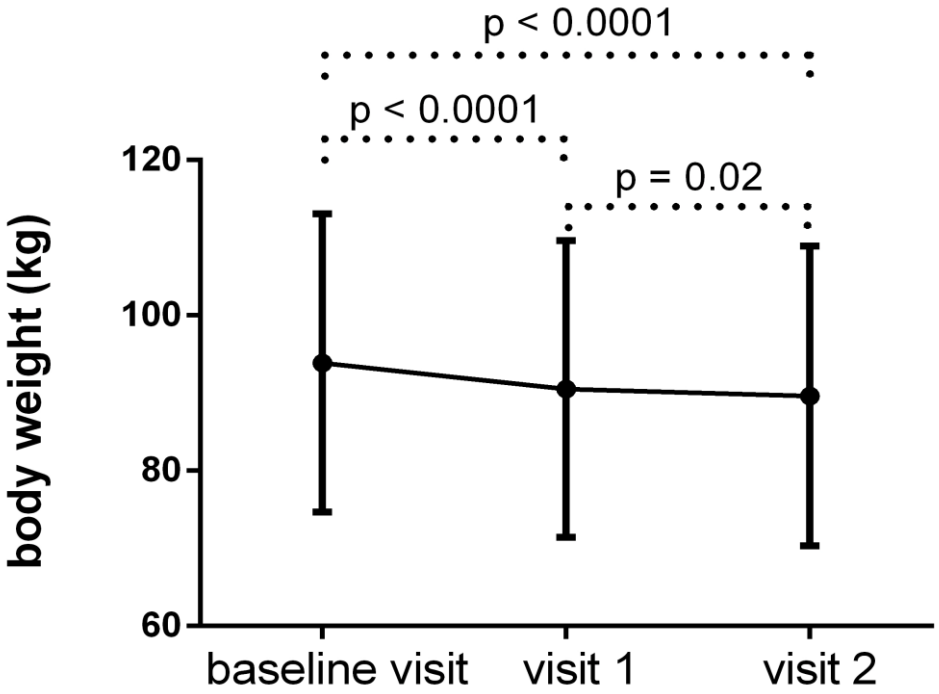


Fig. 8 Body weight (mean±SD) of patients at baseline and 3 and 7 months later

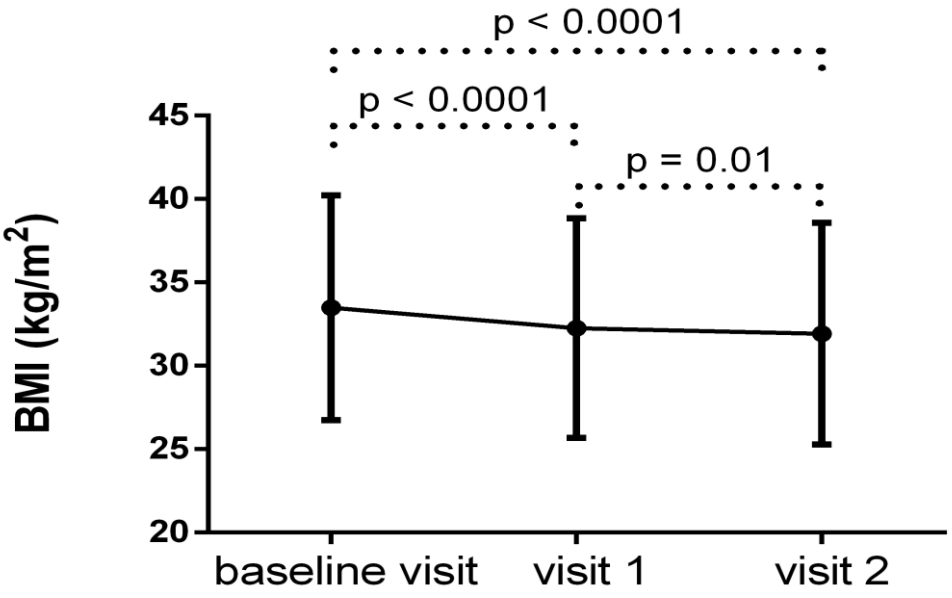


Fig. 9 BMI (mean±SD) of patients at baseline and 3 and 7 months later

IDegLira + metformin combination therapy was safe and generally well tolerated. Transient gastrointestinal adverse events (lack of appetite, abdominal pain, nausea or diarrhoea and in one case vomitus) were reported by 17 patients (25%) and 2 patients (3%) had transient dysthymia. Only two cases of SAE occurred (acute non-ST segment myocardial infarction, and acute peritonitis presented with heart failure due to dilatative cardiomyopathy with intracardiac thrombi) which in our opinion were not related to IDegLira therapy.

During the month before BV 32 patients (47%) had at least one documented (self-measured plasma glucose<3.9 mmol/L) or symptomatic hypoglycemia, while during the 7 month follow-up only 12 patients (18 %) reported 30 documented (1 asymptomatic and 29 mild) episodes in all. Severe hypoglycemia requiring external assistance did not occur (Fig. 10).

Mean daily number of injections changed from 3.75 ± 0.63 to 1, and the patients substantially reduced the daily number of blood glucose testing also.

During the 7 months follow-up 58 patients (85%) lost weight.

At visit 2 the proportions of patients who had achieved $HbA_{1c} \leq 7\%$ and $HbA_{1c} \leq 6.5\%$ were 88% ($n = 60$) and 74% ($n = 50$), respectively (Fig. 11).

The proportions of patients who achieved $HbA_{1c} \leq 7\%$ and $HbA_{1c} \leq 6.5\%$ without any weight gain were 78% ($n = 53$) and 66% ($n = 45$), respectively. The proportions of patients who attained $HbA_{1c} \leq 7\%$ and $HbA_{1c} \leq 6.5\%$ without hypoglycemia were 74 % ($n = 50$) and 59% ($n = 40$), respectively. Finally, the proportions of patients who realized $HbA_{1c} \leq 7\%$ and $HbA_{1c} \leq 6.5\%$ without weight gain and without hypoglycemia were 65% ($n = 44$) and 53% ($n = 36$), respectively.

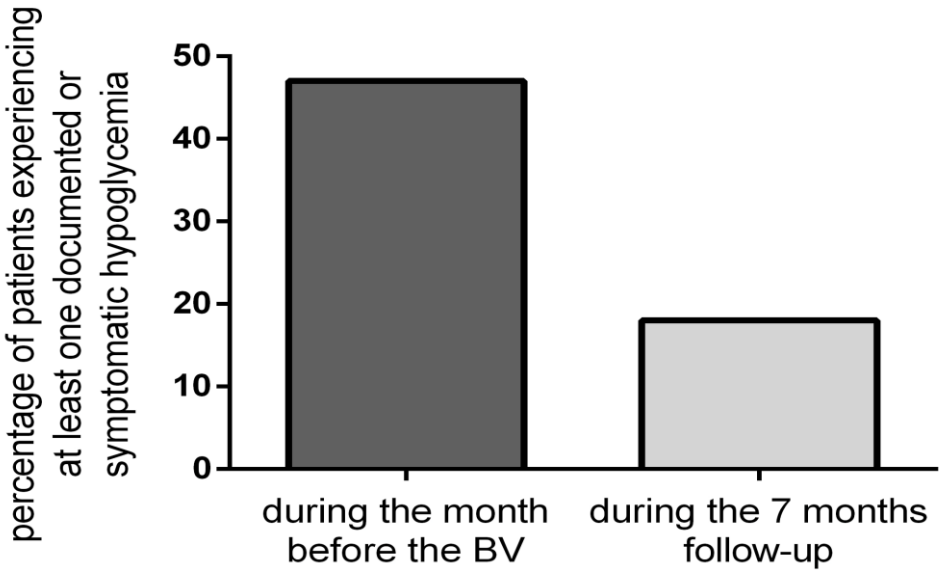


Fig. 10. Incidence of patients with at least one documented hypoglycemia during the month before baseline visit (BV) and during the 7 months follow-up

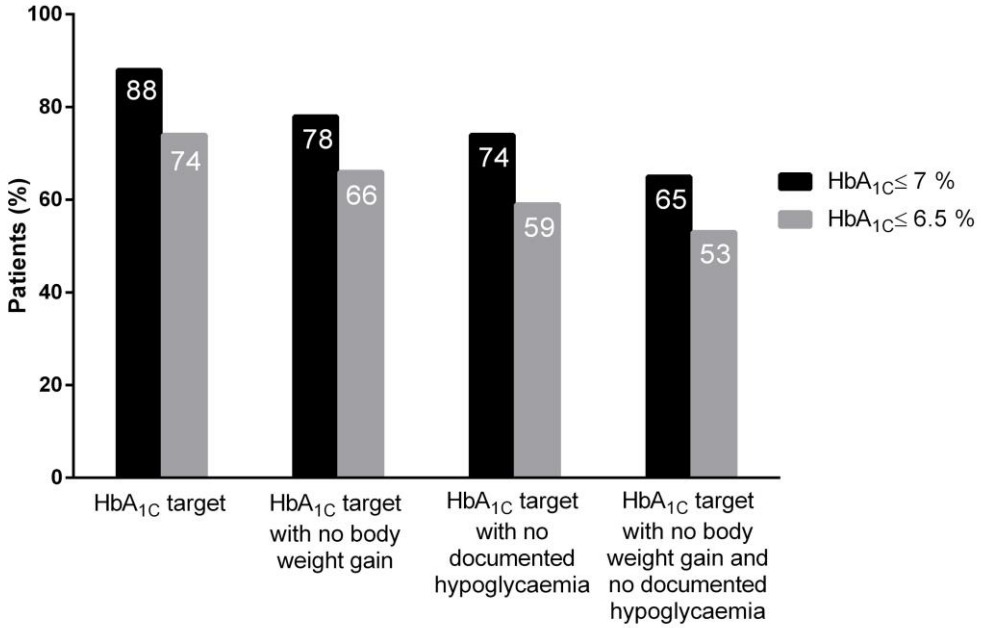


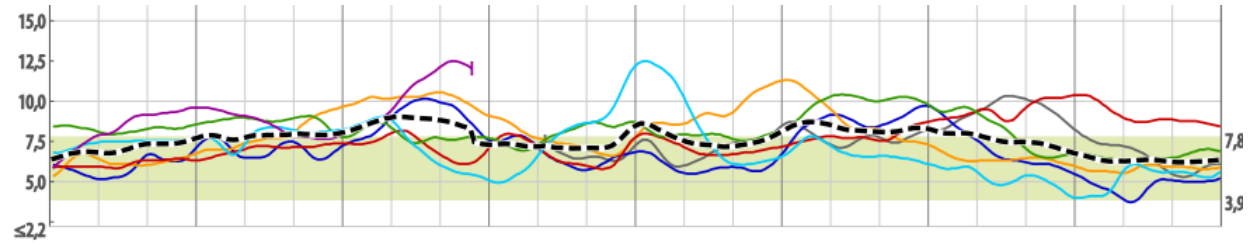
Fig. 11 Proportions of patients who had achieved various glycemic targets at visit 2

Glycemic variability, the degree to which a patient's blood glucose level fluctuates between high and low levels, may be an HbA_{1c}-independent risk factor for diabetes complications and

greater glycemic variability may be associated with lower quality of life and negative moods [23,24,25].

Our clinical experience suggests that de-escalation of MDI with IDeglira can decrease glycemic variability measured by professional CGM (Fig. 12) [20].

A



B

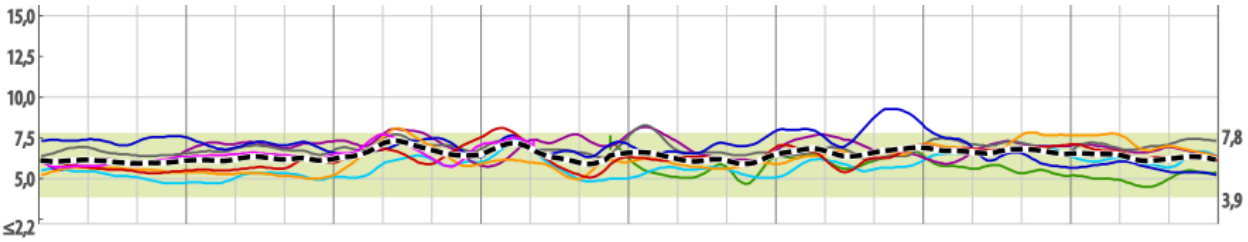


Fig. 12 A: CGM data (mmol/l) of a 67-year old man with type 2 diabetes treated with 3 doses of human regular and one dose of NPH insulin plus 500 mg metformin XR at baseline (HbA_{1c} 6.4%, body weight: 78 kg, body mass index [BMI]: 27.9 kg/m^2, TDD 44 IU/day [0.58 IU/kg]); 24-h SD of the glucose readings is 1.5. **B:** CGM data of the same patient 3 month after simplifying MDI with IDegLira (HbA_{1c} 5.8%, body weight: 70.3 kg, BMI: 25.2 kg/m^2, TDD 24 units of IDegLira [0.34 units/kg]); metformin XR was uptitrated to 1500 mg, 24-h SD of the glucose reading decreased to 0.8.

4. Discussion

Currently 463 million adults are living with diabetes in the World and the IDF estimates that in 2045 this number will be 700 million [1]. Insulin was first used in the treatment of diabetes on 11 January 1922. [26] Although novel glucose lowering agents (e.g. GLP-1 RAs or SGLT2Is)

were introduced in the last decade, insulin used in complex regimens still remained the mainstay of antidiabetic therapy after a hundred years of its discovery in 1921. The major advantage of insulin over other glucose-lowering medications is that it lowers glucose in a dose-dependent manner over a wide range and to almost any glycemic target, but it can increase the risk of hypoglycemia, promote weight gain and cause significant treatment burden for the patients.

In T2D MDI as initial treatment is recommended when blood glucose is ≥16.7 mmol/L or HbA_{1c} is ≥10% or if symptoms of hyperglycemia (i.e., polyuria, polydipsia) are present [3, 27]. As the patient's glucose toxicity resolves, the initially introduced complex regimen may, potentially, be simplified, but there are no specific guidelines regarding deintensification and a lot of patients are left on MDI for years while a significant proportion of them become overtreated [2,3,4].

Actual clinical practice guidelines usually focus on intensifying therapy to achieve target HbA_{1c} levels as soon as possible after the diagnosis. Treatment intensification is the stepwise addition of new non-insulin glucose lowering agents, the initiation of an insulin, or a switch to more complex insulin regimen. As it is clearly proven that long-term intensive glucose control can reduce the risk of diabetes-associated micro- and macrovascular complications, the failure to intensify treatment (clinical inertia) may have a negative impact on patients' outcomes. However in the last couple of years it has been recognised that in certain clinical situations there is need for de-escalation of complex glucose lowering regimens and the delay in simplifying the treatment can also have detrimental consequences for the patients [16,17].

De-escalation of the treatment is reasonable in T2D patients 1) after bariatric surgery, 2) with significant weight loss, 3) with continuously worsening renal functions, 4) with social deprivation 5) in patients who used MDI for a transient reason (surgery, intercurrent illness etc.) but restitution of the former therapy was missed, 6) in social deprivation, 7) and also in patients who are overtreated. In general overtreatment is defined as the use of a treatment even when the potential harms exceed the possible benefits [5].

The patients' conditions play a central role in the success of the therapy therefore the individual general health status and self-management ability should always be taken into account when choosing optimal treatment. Application of an intensive but complex insulin therapy in older patients with several associated comorbidities might result perfect HbA_{1c} levels but increase

the risk of hypoglycemia and weight gain and it's adherence causes unnecessary treatment burden and worsens their quality of life [6, 28]. This kind of overtreatment is detrimental for most of the patients [17]. In line with this, the latest guidelines nowadays recommend deintensification of treatment regimens in older, frail adults with T2D but it is obvious that overtreatment can happen in any age group [4].

It is generally accepted that older and younger patients as well are overtreated if they are treated too aggressively and their HbA_{1c} is permanently under the individually defined optimal target ranges (overtreated, overcontrolled patients).

Recent studies suggest that this type of overtreatment is a common and generally unrecognized problem among patients with T2D, but rates of medication deintensification in everyday clinical practice are low and evidence-based strategies for the prevention of overtreatment and simplification of therapy are yet to be devised [6,7,8,10,11]. Recently our survey conducted at Békéscsaba, Hungary also demonstrated that overtreatment is a common problem. According to our results 34.5% of the T2D patients aged over 75 years treated with hypoglycemic agents were potentially overtreated and 70% of the overtreated individuals had intermediate or poor health status [9].

Another form of overtreatment is when well-controlled T2D patients are treated with unnecessarily complex regimens instead of simpler alternatives ensuring the same glycemic control with less treatment burden and side effects (overtreated, well-controlled patients).

In general the implements of treatment deintensification in T2D includes dosage reduction, the discontinuation of a medication and the simplification of complex regimens. Very few studies enrolling a small number of older T2D patients treated with hypoglycemic medications have examined the outcomes of deintensification regimens, and there were no published data about the process of simplifying MDI regimens in well-controlled people with T2D [15].

The aim of our real-world prospective study was to examine the safety and efficacy of switching from MDI to once daily IDegLira in relatively well controlled ($HbA_{1c} \leq 7.5\%$) subjects with T2D using low TDD. At baseline most of the patients using complex insulin regimens who were enrolled in our study had optimal glycemic control. Medication simplification was performed in those cases to decrease treatment burden and to improve quality of life. However, as some

of our patients had HbA_{1c} values that were too low, leading to high risk of hypoglycemia, reducing the frequency of hypoglycemia and achieving appropriate glycemic control were also objectives.

The results of a one-arm intervention study enrolling elderly T2D patients (n=65, baseline HbA_{1c} 7.7%) with one or more episodes of hypoglycemia confirmed with CGM demonstrated that switching MDI to a single dose of basal insulin (glargine U100) combined with non-insulin glucose-lowering agents if required can decrease the risk of hypoglycemia and disease-related distress without compromising glycemic control [14].

In our study, instead of a single long-acting basal insulin, we used IDegLira (a fixed-ratio combination of a long-acting basal insulin and a GLP-1-RA) for medication deintensification because it was demonstrated that IDegLira produces significantly greater improvement in overall glycemic control than a basal insulin (due to the fasting and prandial effects of liraglutide) as well as significantly reduced frequency of confirmed hypoglycaemia and a more favourable effect on body weight [29, 30].

Compared to high-dose monotherapies of the two components, we use lower doses of both degludec and liraglutide in the fixed-ratio combination, which can result in lower risk of adverse effects.

Other works in the literature also encouraged us to use IDegLira to simplify MDI. For instance, the DUAL (Dual Action of Liraglutide and Insulin Degludec in Type 2 Diabetes) VII randomised clinical trial demonstrated that IDegLira exerts comparable glycemic effects to MDI on patients with uncontrolled T2D who are on glargine U100 plus metformin. That trial showed that IDegLira provided lower hypoglycemia rate and weight loss versus weight gain compared to MDI treatment [18]. In addition, the cardiovascular outcome trials LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) and DEVOTE (A Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events) confirmed the cardiovascular benefits and safety of liraglutide and degludec [31, 32].

C-peptide is a commonly used measure of pancreatic beta cell function. It is produced in equimolar amounts to endogenous insulin but is excreted at a more constant rate over a longer

time [33]. In a retrospective study serum C-peptide level was used successfully to guide the simplification of insulin regimen in older adults with T2D (n=36) who had poor glycemic control or difficulty coping with complicated regimens, and simplification resulted in better glycemic control and less hypoglycemia [34]. We only included patients into our study with detectable levels of C-peptide.

One of the analysed descriptive parameters in our study was the follow-up of TDD. Average daily insulin production of healthy men is about 0.7-0.8 IU/kg. Mean TDD in T2D can vary considerably with the level of insulin resistance and residual beta-cell function, but Caucasian patients treated with MDI regimens usually have a TDD between 0.9 and 1.4 unit/kg [18,35,36].

We supposed that a normal or near normal HbA_{1c} achieved with a low TDD is associated with some degree of preserved endogenous insulin secretion. We defined a low insulin need as an average TDD≤0.6 IU/kg of body weight and used this definition together with the positive C-peptide level to identify potential candidates for our study.

The safety of our patients was ensured by the study design as the maximal daily dose of iDeglira was 50 units, and we only enrolled patients with a TDD≤70 units/day at BV to be able to cover the effects of the previous complex regimens.

In our first analysis we reported the short-term (3 months) follow-up data of 62 well-controlled (or overcontrolled) T2D patients whose low dose MDI regimens were switched to IDegLira [19]. Our preliminary data demonstrated the very first time that in everyday clinical practice de-escalation of MDI regimens with IDegLira in selected T2D patients is feasible and safe. We described the characteristics of those well-controlled T2D patients who are eligible for a successful treatment deintensification. Furthermore we showed that on short-term the simplified treatment conferred similar or better glycemic control with less hypoglycemia and weight loss versus weight gain compared to the MDI regimens used previously.

According to our observations the process of de-escalation and the IDegLira+metformin combination therapy was safe and generally well tolerated. Transient non-serious gastrointestinal adverse events (lack of appetite, nausea or diarrhoea) were reported by 14 patients (22.5%) and 1 patient had transient dysthymia. The incidence and severity of these digestive symptoms are similarly described in the literature with the same transient nature [18].

During the 3-months follow-up only one SAE occurred (acute non-ST segment myocardial infarction) which in our opinion was not related to iDegLira therapy.

Besides demonstrating in everyday clinical practice the feasibility and safety of switching MDI to IDegLira we wanted to describe the characteristics of those otherwise well-controlled T2D patients who are treated with MDI but are eligible for medication simplification as well. We confirmed that simplification of complex insulin regimens can be performed successfully in adult T2D patients who have an $HbA_{1c} \leq 7.5\%$, treated with low dose (TDD≤0.6 IU/kg and TDD≤70 IU/day) MDI, and have a detectable (≥1.1ng/mL) random, non-fasting serum C-peptide level, indicating that there is some degree of preserved endogenous insulin secretion. We were looking for well-controlled patients, but we found that some of our enrolled patients were overcontrolled, as they were treated too aggressively and had HbA_{1c} values below the optimal target range, leading to a high risk of hypoglycemia.

After a mean follow-up of 99.2 days, HbA_{1c}, body weight, and BMI had decreased significantly. Mean HbA_{1c} decreased by 0.30% to 6.12 ± 0.65% ($p < 0.0001$), body weight decreased by 3.11 kg to 90.70 ± 19.12 kg ($p < 0.0001$), and BMI decreased to 32.39 ± 6.71 kg/m^2 ($p < 0.0001$).

Despite the low baseline TDD, the combined application of degludec and liraglutide resulted in a further reduction of TDD and a proposed glycemic control. At BV TDD was 43.31 ± 10.99 IU/day whilst the mean dose of IDegLira at visit 1 was only 20.76 ± 6.60 units (the mean dose of liraglutide was 0.75 mg), meanwhile the median dose of metformin increased from 1500 [0–2000] mg to 2000 [1000–2000] mg. The mean insulin requirement decreased from 0.47 ± 0.23 IU/kg at baseline to 0.23 ± 0.08 IU/kg at visit 1. There are two main explanations for the insulin sparing-effects of liraglutide. On the one hand liraglutide has a strong glucose-lowering effect deriving from the glucose-dependent enhancement of insulin secretion and inhibition of glucagon secretion. On the other hand, substantial weight loss is associated with liraglutide treatment, leading to a lower insulin requirement

De-escalation of MDI regimens with IDegLira performed in the eligible overtreated T2D patients led to substantially reduced risk of hypoglycemia. During the month before BV, 28 patients (45%) had at least one episode of documented (self-measured plasma glucose < 3.9 mmol/L) or symptomatic hypoglycemia, while only 6 (9.67%) patients reported a total of 13 documented episodes during the 3 months follow-up. Severe hypoglycemia requiring external

assistance did not occur. At the 3-months visit the proportion of patients achieving an HbA_{1c} ≤7% was 92% moreover 73% reached that target without weight gain or hypoglycemia.

Our first observations were very promising, but we wanted to confirm the results over a longer follow-up period and in a larger group of patients. In our subsequent analysis we reported longer-term (7 months) follow-up data of 69 well-controlled (or overcontrolled) T2D patients whose MDI regimens were de-escalated with IDegLira. [21]

The results of the 7-month follow-up unambiguously confirmed the conclusions derived from our shorter-term follow-up data, that in everyday clinical practice switching from low dose MDI to IDegLira in selected well-controlled or overcontrolled T2D patients is safe, may induce weight loss, results in similar glycemic control and associated with substantially reduced insulin requirement and lower risk of hypoglycemia.

Our longer-term observations further supported that de-escalation with IDegLira is safe and the treatment is generally well tolerated. Transient gastrointestinal adverse events (lack of appetite, abdominal pain, nausea or diarrhoea and in one case vomitus) were reported by 17 patients (25%) and 2 patients (3%) had transient dysthymia. Only two cases of SAE occurred which in our opinion were not related to iDegLira therapy.

We managed to preserve good glycemic control and substantially decreased the risk of hypoglycemia. After a mean follow-up of 220 days HbA1c changed from 6.36 ± 0.71% at BV to 6.20 ± 0.64% at Visit 2 (estimated mean difference -0.16% [-0.33 - 0.01], p=0.07). During the month before BV 32 patients (47%) had at least one documented or symptomatic hypoglycemia, while during the 7 month follow-up only 12 patients (18%) reported 30 documented episodes in all. No severe hypoglycemia requiring external assistance did occur.
The therapeutic success was also observed in significant weight loss during the 7 months follow-up. Body weight decreased from 93.88 ±19.18 kg to 89.61 ± 19.31 kg (estimated mean difference -4.27 [-5.65 – -2.89], p<0.0001) and BMI changed from 33.48 ± 6.73 kg/m2 to 31.93 ± 6.64 kg/m2 (estimated mean difference -1.55 [-2.04 – -1.06], p<0.0001]).

Insulin requirement decreased by almost 50% from BV to visit 1 and remained near the same at visit 2. At BV TDD was 43.77 ± 11.3 IU/day, whilst after 7 months of follow-up mean dose of IDegLira was 21.44 ± 7.64 units (mean dose of liraglutide was 0.77 mg). Median dose of

metformin increased from 1600 mg to 2000 mg, and mean insulin requirement decreased from 0.47 ± 0.12 IU/kg to 0.24 ± 0.08 IU/kg.

The benefits of de-escalation were emphasized by the fact that at the 7-months visit the proportion of patients achieving an HbA_{1c} ≤7% was 88% and 65% reached that target without weight gain or hypoglycemia.

According to our results measuring HbA_{1c}, C-peptide and calculation of TDD can help clinicians in identifying well-controlled but overtreated patients who will benefit from medication deintensification. We showed that switching MDI to IDegLira is feasible as our selected overtreated patients achieved similar or better HbA_{1c}, had fewer hypoglycemia, lost weight and used only one injection daily with IDegLira compared to the previously used complex insulin regimens. Our observations support facts about the putative long-term benefits of the combined liraglutide-degludec treatment over MDI therapy. On one hand the achievement of the target HbA_{1c} levels may ensure the lower risk of microvascular complications and the observed weight loss complements the beneficial effects on insulin sensitivity. On the other hand applying IDegLira instead of MDI regimens can be more advantageous, because the achieved good glycemic control, weight loss and reduced hypoglycemia risk coupling with the proven cardiovascular benefits of degludec and liraglutide may confer lower risk of macrovascular complications on long term. Furthermore, the once versus two-to-four times injection and the lower risk of hypoglycemia appreciably improves quality of life and adherence to therapy.

To the best of our knowledge we suggested first that those well-controlled T2D patients who have positive C-peptide values and use low dose MDI regimens should be considered overtreated and their complex treatment regimens should be de-escalated, because there are simpler treatment alternatives which can ensure the same glycemic control with less treatment burden. We demonstrated first that in selected T2D patients de-escalation of low dose MDI regimens with IDegLira, a fixed ratio combination of insulin degludec and liraglutide is feasible and safe. Furthermore we showed that on short-term and on longer-term the simplified treatment confers similar or better glycemic control with less hypoglycemia and weight loss versus weight gain compared to the MDI regimens used previously.

Our real-world setting prospective before-after study has several limitations. It was a non-randomised, non-blinded, uncontrolled, one-centered study. The sample size remained relatively low. Besides the initiation of IDegLira the titration of metformin also affected the HbA_{1c} efficacy achieved. We are not able to estimate separately the effects of IDegLira and metformin, anyway our goal was not to test a certain drug but to study the strategy of de-escalation.

As glycemic variability may be an HbA_{1c}-independent risk factor for diabetes associated complications and greater glycemic variability may be associated with lower quality of life and negative moods, reducing the magnitude of this factor may result in several clinical benefits. [23,24,25]. Our initial experience suggests that de-escalation of MDI with IDeglira can decrease glycemic variability measured by professional CGM in selected T2D patients [20]. In one of our presented case IDegLira markedly reduced both intra-day and inter-day glycemic variability described by the 6-day CGM data compared to the previously used basal-bolus regimen. (Fig 12). In the future we are planning to enroll more patients to the CGM subgroup of our study to be able to analyse the effect of de-escalation on glycemic control and variability and quality.

5. Conclusions and new findings

I. Well-controlled T2D patients who are using unnecessarily complex insulin regimens instead of simpler alternatives which would ensure the same glycemic control with significantly less treatment burden should also be considered overtreated.

II. Measuring HbA_{1c}, C-peptide and calculation of TDD can help clinicians in identifying well-controlled but overtreated patients who will benefit from medication deintensification. Simplification of complex insulin regimens can be performed successfully in adult T2D patients who have an $HbA_{1c} \leq 7.5\%$, treated with low dose MDI, and have a detectable random, non-fasting serum C-peptide level.

III. In everyday clinical practice, switching the eligible well-controlled (or overcontrolled) T2D patients of different ages from MDI to IDegLira, a fixed ratio combination of insulin degludec and liraglutide is feasible and safe.

IV. De-escalation of MDI regimens with IDegLira in the selected overtreated T2D patients ensures similar or better glycemic control and may induce weight loss.

V. De-escalation of MDI regimens with IDegLira performed in the eligible overtreated T2D patients leads to substantially reduced insulin requirement and a reduced risk of hypoglycemia.

VI. De-escalation of complex insulin regimens with IDegLira decreases treatment burden and may improve adherence to therapy.

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